
2012 Pharmacology Risk Standing Review Panel

Research Plan Review for: *Risk of Clinically Relevant Unpredicted Effects of Medication*

Final Report

I. Executive Summary and Overall Evaluation

The 2012 Pharmacology Risk Standing Review Panel (from here on referred to as the SRP) participated in a WebEx/teleconference with representatives from the Human Research Program (HRP) Human Health Countermeasures Element and HRP management (list of participants is in Section VI of this report) on December 19, 2012 to review the Research Plan for the Risk of Clinically Relevant Unpredicted Effects of Medication in the Human Research Program's (HRP) Integrated Research Plan (IRP Rev. D).

Overall, the SRP believes that the research plan described in the IRP Rev. D demonstrates good progress since the most recent (2011) Pharmacology Risk SRP meeting. The organization of research plan is improved, and the description of the risks, tasks, gaps is more clearly written. Many of the changes are in response to and in accord with the comments by the 2011 Pharmacology Risk SRP. The SRP believes, however, that the tasks need to be prioritized by risk, and a more detailed description of each task is needed so that there is a general agreement that the task will indeed accomplish its objective. The SRP also continues to urge setting up a process for inventory of the in-flight medication used by astronauts ("pharmacology database", see below) as a way to help accomplish this prioritization.

The SRP furthermore concluded that an area for potential integration across disciplines is the completion of this pharmacology database. This pharmacology database could be integrated with other tools such as the Medication and Symptom Tracking Tool, the Food and Drug Administration (FDA) Adverse Event Report Monitoring; a comprehensive in-flight drug formulary is equally important. The database will need to be regularly reviewed, updated and analyzed to determine whether the most effective medications are still being used and whether there are potential areas of concern for changes in drug safety/efficacy. The database should be capable of data mining for various research and statistical needs.

II. Critique of Gaps and Tasks for the Risk of Clinically Relevant Unpredicted Effects of Medication

Gaps and Tasks:

Pharm01 (formerly PH01): We do not know how medications are used during spaceflight.

- The SRP thinks this is a relevant gap.

Task:

- Pharmacology Database – Planned task
 - The SRP thinks that this is the most important task. This pharmacology database
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- should be an ongoing effort that contains historical medication use data (as available/accessible), current data and new data going forward. Decisions need to be made concerning which specific information is to be included in the database and how to organize of the database. Moreover, the database needs to be reviewed on a regular basis to determine which data is still relevant and whether new data need to be included. The database could be in an electronic format with hyperlinks to various sections. The database should be capable of data mining for various research and statistical needs.
- The SRP thinks that several additional sections might be included in the pharmacology database: For example, a Drug Formulary for the astronauts could be included as a subsection of the pharmacology database. The drug formulary would list the drugs that are taken into space and may include the drug, dose, adverse events, contraindications, drug interactions, expiration date, lot number, etc. Since there is the possibility that the expiration for some of the drugs may occur in space, there could be an indication as to the risk in taking a drug past the manufacturer's expiration date (see below).
 - In-Flight Medication Utilization Data Mining – Planned task
 - This SRP thinks this task is extremely useful and could be linked to the Medication and Symptom Tracking Tool. It would be of interest to know the nature and severity of the symptoms that caused the astronaut to take the medication of interest. Where there are multiple drugs for a similar effect (e.g., analgesics), how is the choice of medication decided? For example, how do the astronauts chose between using acetaminophen rather than a non-steroidal anti-inflammatory drug (NSAID)? Will the astronauts have the independence and knowledge to make these choices?
 - Medication and Symptom Tracking Tool – Planned task
 - The SRP thinks that the information gained from the task could be helpful in the determination of pharmacodynamics (PD) in spaceflight (see Pharm04). Do the astronauts obtain the same efficacy and safety including onset, duration of action from the medications as do people on earth? Is there is a difference between amelioration of symptoms in space versus on Earth?
 - Clinical Trial and FDA Approved Technology Watch – PI: Virginia Wotring, Ph.D., NASA Johnson Space Center
 - FDA Adverse Event Report Monitoring – Planned task
 - The SRP thinks that this task might be incorporated into the pharmacology database along with the Medication and Symptom Tracking Tool. As stated above, both the tasks may be related to changes in PD activity of the drug. For example, are adverse events in space more frequent and/or more severe than observed on Earth?

Pharm02 (formerly PH09): We do not know how long medications may be safe and effective beyond their expiration dates.

- The SRP is unsure whether and, or how this gap should be explored at this time, given the reported operational constraints. The slide presented during the review on this gap states that the gap “...is largely unknown, and the issue has been operationally avoided by continuous replenishment of supplies.” Therefore, the SRP thinks that with minimal cost, as compared to performing expensive stability testing, the Pharmacology discipline

has been able to mitigate the risk. The SRP suggests putting a lower priority on this risk or even taking it out, until there is more information on any clinically meaningful PK/PD changes during spaceflight, which will help risk-based prioritization of any in-flight or terrestrial drug stability testing.

Tasks:

- FDA Comprehensive Stability Evaluation of Three Medications – Planned task
- Packaging Tech Watch – Planned task
- Evaluation of Packaging Materials and Methods for Improved Medication Stability – Planned task
- In-Flight Medication Stability Analysis Method – Planned task
- Stability Analysis of ISS Medications – Planned task
- Pharmacology Database – Planned task

The SRP agrees with these tasks. It may be possible to obtain stability data from the manufacturers and to determine which drugs may be most prone to instability. The manufacturers may also have information as to the nature of the degradation processes and products and whether the drug product, if used beyond the expiration label, pose any hazard for use by the astronaut even though the drug product might be subpotent. If the latter is true, the astronaut then could adjust the dose upward of the expired drug product to achieve the intended efficacy.

Pharm03 (formerly PH07 & PH10): We do not know the extent to which spaceflight alters pharmacokinetics.

Tasks:

- Effect of Spaceflight on Expression of Metabolic Enzyme Genes in Mice – PI: Virginia Wotring, Ph.D., NASA Johnson Space Center
- Validation of Salivary Sampling for Pharmacokinetic Studies – Planned task
- PK Probes in Spaceflight – Planned task
- PK in Spaceflight: Follow-on Study – Planned task
 - The pharmacology database should provide PK information, including presence and significance of any active metabolite(s), for each drug taken in spaceflight. From these drugs, it is needed to ascertain which drugs would have efficacy/safety issues if the PK for these drugs were to change significantly in space.
 - Salivary drug concentrations do not always relate to plasma drug concentration profiles. An alternative PK approach is to introduce a test drug with well described PK and whose salivary drug concentrations directly relate to the PK profile obtained from blood samples. PK changes in the test drug may predict PK changes in drugs of similar class. Another non-invasive method is to determine drug excretion in urine. For PK analysis, this method works better for drugs that are excreted normally in high concentrations as the unchanged drug. Urinary drug excretion can also be used for the determination of biotransformation (metabolism).
- Effects Of Radiation and Dietary Iron on Expression of Genes and Proteins Involved In Drug Metabolism – PI: Virginia Wotring, Ph.D., NASA Johnson Space Center
 - The SRP noted that it may be very difficult to extrapolate any *in-vitro* or *in-vivo*

metabolic findings from non-human animal species to humans is difficult and fraught with unknowns. A non-invasive approach to determine whether drug metabolism is changing in spaceflight is to obtain a post drug dose urine sample from which the ratios of metabolites to unchanged drug in spaceflight may be compared to on land. If these ratios are changing then the rates of metabolism are changing. These findings would be much more relevant to make any therapeutic recommendations.

- In-Flight Medication Utilization Data Mining – Planned task
- Pharmacology Database – Planned task
- Clinical Trial and FDA Approved Technology Watch – PI: Virginia Wotring, Ph.D., NASA Johnson Space Center
- FDA Adverse Event Report Monitoring – Planned task
- Medication and Symptom Tracking Tool – Planned task

Pharm04 (formerly PH07 & PH10): We do not know the extent to which spaceflight alters pharmacodynamics.

Tasks:

- PD in Spaceflight – Planned task
 - The SRP thinks that PD changes in flight might be difficult to determine directly. Such direct methods are usually more accurate for acute pharmacodynamic endpoints such as skin blanching due to corticosteroids, changes in forced expiratory volume in one second (FEV1) due to bronchodilators, etc. Whether PD changes are clinically important may depend upon the steepness of the log drug dose or plasma concentration versus response curve and the potency of the drug.
- Pharmacology Database – Planned task
- In-Flight Medication Utilization Data Mining – Planned task
- Effects Of Radiation and Dietary Iron on Expression of Genes and Proteins Involved In Drug Metabolism – PI: Virginia Wotring, Ph.D., NASA Johnson Space Center
- Clinical Trial and FDA Approved Technology Watch – PI: Virginia Wotring, Ph.D., NASA Johnson Space Center
- FDA Adverse Event Report Monitoring – Planned task
- Medication and Symptom Tracking Tool – Planned task
 - As mentioned above, the Medication and Symptom Tracking Tool and the FDA Adverse Event Report Monitoring could be indirect approaches for the determination of PD in spaceflight. Both tasks are related to drug safety and, or efficacy and PD activity of the drug. Is there any evidence of statistical differences in adverse events rates in space compared to the rates observed on Earth? Do the astronauts obtain the same efficacy and safety including onset, duration of action from the medications as do people on Earth? Is there is a difference between amelioration of symptoms in space versus on Earth?

Pharm05 (formerly PH15): We do not know the extent to which current antimicrobial therapies are effective against microbes that have been altered by spaceflight.

- The SRP gives this gap a very high priority, given that the impact of any development of resistance by microorganisms to antimicrobials would be clinically and operationally

important in space.

Tasks:

- Efficacy of Antimicrobials on Bacteria Cultured in a Spaceflight Analog – PI: Mark Ott, Ph.D., NASA Johnson Space Center
- Full Scale Antimicrobial Screening – Planned task
- Flight Antimicrobial Screening – Planned task
- Pharmacology Database – Planned task
- In-Flight Medication Utilization Data Mining – Planned task
- Clinical Trial and FDA Approved Technology Watch – PI: Virginia Wotring, Ph.D., NASA Johnson Space Center
- FDA Adverse Event Report Monitoring – Planned task
- Medication and Symptom Tracking Tool – Planned task

III. Discussion on the strengths and weaknesses of the IRP and identify remedies for the weaknesses, including answering these questions:

Is the Risk addressed in a comprehensive manner?

- Overall the SRP thinks that the risk has been addressed in a comprehensive manner. Further efforts are needed for a rational, risk-based prioritization of the various tasks, especially information about the in-flight drug formulary and medication use by the astronauts.

Are there obvious areas of potential integration across disciplines that are not addressed?

- The pharmacology database with the integration of this database with other tools such as the Medication and Symptom Tracking Tool, the FDA Adverse Event Report Monitoring and a comprehensive drug formulary is important. The database will need to be regularly reviewed, updated and data analyzed to determine whether the most effective medications are being used and whether there are potential areas for changes in drug safety and/or efficacy.
- As discussed during the WebEx/teleconference review, the SRP thinks that better coordination between the physicians who are responsible for the astronauts' health and the members of the pharmacology discipline is needed in order to get better information on the medications used by the astronaut in-flight. Once this relationship is established, the next steps could be to explore dose-response relationships, especially with chronic conditions such as hypertension, hypercholesterolemia, etc. If this reveals information that indicates some adverse impact on safety and, or efficacy of the medication, perhaps a prospectively designed sparse sampling study could be undertaken to characterize the relationship.

IV. Evaluation of the progress in the IRP Rev. D since the 2011 SRP meeting.

- The IRP Rev. D shows major progress since the 2011 Pharmacology Risk SRP. The organization of IRP Rev. D is better and description of the risks, tasks, gaps is more clearly written. Many of the changes are in response to and in accord with the comments by the 2011 Pharmacology Risk SRP.

V. 2012 Pharmacology Risk SRP Research Plan Review (WebEx): Statement of Task for the Risk of Clinically Relevant Unpredicted Effects of Medication

The 2012 Pharmacology Risk Standing Review Panel (SRP) is chartered by the Human Research Program (HRP) Chief Scientist. The purpose of the SRP is to review the Human Health Countermeasures (HHC) Element's section of the HRP's Integrated Research Plan, Revision D (IRP Rev. D) which is located on the Human Research Roadmap (HRR) website (<http://humanresearchroadmap.nasa.gov/>). Your report will be provided to the HRP Chief Scientist.

The 2012 Pharmacology Risk SRP is charged (to the fullest extent practicable) to:

1. Evaluate the ability of the IRP Rev. D to satisfactorily address the Risk by answering the following questions:
 - A. Have the proper Gaps been identified to address the Risk?
 - i) Are all the Gaps relevant?
 - ii) Are any Gaps missing?
 - B. Has the appropriate target for closure for the Gap been identified?
 - i) Are the interim stages appropriate to close the Gap?
 - C. Have the proper Tasks been identified to fill the Gaps?
 - i) Are the Tasks relevant?
 - ii) Are any Tasks missing?
2. Identify the strengths and weaknesses of the IRP Rev. D, *and* identify remedies for the weaknesses, including answering these questions:
 - A. Is the Risk addressed in a comprehensive manner?
 - B. Are there obvious areas of potential integration across disciplines that are not addressed?
3. Please evaluate the progress in the IRP Rev. D since your 2011 SRP meeting.
4. Please comment on any important issues that are not covered in #1, #2, or #3 above.

Additional Information Regarding This Review:

1. Expect to receive review materials at least four weeks prior to the WebEx conference call.
2. Participate in a WebEx conference call on December 19, 2012.
 - A. Discuss the 2012 Pharmacology Risk SRP Statement of Task and address questions about the SRP process.
 - B. Receive presentations from the HHC Element.
 - C. Participate in a question and answers session.
 - D. Attend Element or Project presentations, question and answer session, and briefing.

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3. Prepare a draft final report (within one month of the WebEx/teleconference) that contains a detailed evaluation of the current IRP specifically addressing items #1, #2, #3, and #4 of the SRP charge. The draft final report will be sent to the HRP Chief Scientist and he will forward it to the appropriate Element for their review. The HHC Element and the HRP Chief Scientist will have 10 business days to review the draft final report and identify any misunderstandings or errors of fact and then provide official feedback to the SRP. The SRP will have 10 business days to address any issues and finalize the 2012 SRP Final Report. The 2012 SRP Final Report will be submitted to the HRP Chief Scientist and copies will be provided to the HHC Element and also made available to the other HRP Elements. The 2012 SRP Final Report will be made available on the Human Research Roadmap public website (<http://humanresearchroadmap.nasa.gov/>).

VI. 2012 Pharmacology Risk SRP Research Plan Review WebEx/Teleconference Participants

SRP Members:

Jurgen Venitz, M.D., Ph.D. (Chair) – Virginia Commonwealth University
Suresh Mallikaarjun, Ph.D., FCP - Otsuka Pharmaceutical Development & Commercialization, Inc.
Leon Shargel, Ph.D. – Applied Biopharmaceutics, LLC

NASA Johnson Space Center (JSC):

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NASA Research and Education Support Services (NRESS):

Tiffin Ross-Shepard

VII. 2012 Pharmacology Risk Standing Review Panel Roster

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